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Molecular Docking: Applications and Its Challenges

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ABSTRACT

Molecular Docking is the computational modeling of the structure of complexes formed by two or more interrelating molecules. The aim of molecular docking is the prediction of the three-dimensional structures of importance. Molecular docking is a kind of bioinformatic modeling which includes the interaction of two or more molecules to give the constant adduct. Depending upon binding properties of ligand and target, it predicts the three-dimensional structure of any complex. Molecular docking produces various possible adduct structures that are ranked and grouped together using scoring function in the software. In spite of all possible approaches, ligand chemistry (tautomerism and ionization), receptor flexibility (single conformation of rigid receptor) and scoring function (differentiate true binding mode) still persisted the challenge. The vital aspects of molecular docking in its applications and challenges are briefly discussed in this article.

Keywords: docking, conformation, ligand, receptor, optimization

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INTRODUCTION

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. Lead optimization – docking can be used to predict in where and in which relative orientation a ligand binds to a protein. In the field of molecular modeling, molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex [1]. Knowledge of the desired orientation is used to predict the strength of association or binding affinity between two molecules using scoring functions. The relations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play central role in signal transduction [1].

Additionally, the relative orientation of the two interacting partners may affect the type of signal produced (*e.g.* antagonism). Thus docking is beneficial for predicting both the strength and type of signal produced. Docking is normally used to predict the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity of the small molecule. Therefore docking plays a significant role in the rational design of drugs. The goal of molecular docking is to attain an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized [1].

Molecular recognition plays a main role in stimulating fundamental biomolecular events such as enzyme- substrate, drug-protein and drug-nucleic acid interactions. Detailed understanding of the general principles that govern the nature of the interactions (van der Waals, hydrogen bonding, electrostatic) between the ligands and their protein or nucleic acid targets

may provide a outline for designing the desired effectiveness and specificity of potential drug leads for a given therapeutic target. Practical application of this knowledge requires structural data for the target of interest and a procedure for evaluating candidate ligands. Over the last few years a vast amount of effort has been directed for developing well-organized docking methods and scoring functions as tools for the identification of lead compounds. Significant progress has been made in the computational prediction of ligand target binding modes [1].

APPLICATIONS OF MOLECULAR DOCKING

Molecular docking can prove the feasibility of any biochemical reaction as it is carried out before experimental part of any investigation. There are some areas, where molecular docking has developed the findings. In certain, interaction between small molecules (ligand) and protein target (may be an enzyme) may predict the activation or inhibition of enzyme. Such type of information may provide a raw material for the rational drug designing.

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in antagonism. Docking is most frequently used in the field of drug design. Most drugs are organic molecules. Some of the major applications of molecular docking are described below [2].

- **Hit identification:** Docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest [3].
- **Lead optimization:** docking can be used to predict in where and in which relative orientation a ligand binds to a protein (i.e. binding mode or pose). This information may in turn be used to design more potent, selective analogs and efficient drug candidates [4].
- **Bioremediation:** Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes. In contrast to proteins, nucleic acids have received much less attention as drug targets [5].
- **Drugs known to interact with DNA include:** Groove binders (daunomycin), intercalators (actinomycin) and alkylating agents (cisplatin). The variability in DNA structures is relatively small. The folds observed in RNA structures such as ribozymes and ribosomes, comparable in complexity to those of proteins, make RNA attractive as drug targets [6].

Very little effort has been devoted to the rational design of ligands for RNA targets. In the last few years a number of crystal and NMR structures of interesting RNA drug targets have given the idea in the literature.

An important difference between protein and RNA targets relates to binding pocket location. In case of proteins the binding pocket typically lies rather deep in the interior region and the cavity is well separated from solvent.

In RNA targets the binding pocket is located along the surface and is therefore relatively exposed to solvent. The highly charged nature of the target RNA phosphate backbone requires that electrostatic interactions be handled more accurately than typically needed for proteins. Based on DOCK screening aminoglycosides are identified and capable of binding with RNA duplex but not the DNA [7].

CHALLENGES IN MOLECULAR DOCKING

There are certain challenges in docking and scoring is discussed below.

- **Ligand Chemistry**

The ligand preparation has noticeable effect on the docking results because the ligand recognition by any biomolecule depends on 3-dimensional orientation and electrostatic interaction. This confirms that the conformation of both the ligand as well as ligand preparation is important. Earlier, keeping approximate pKa values, the structure being most likely optimized by removing or adding hydrogens but the tautomeric and protomeric states of the molecules which are to be docked, still remained a major discrepancy. Since almost all databases keep molecules in their neutral forms but under physiological conditions they are actually ionized. Hence it is compulsory to ionize them prior to docking. But in different programs, the standard ionization is easy to achieve. Regarding the issue of tautomers, the problem still remains there, which tautomer one should use or should one use all possible tautomers [8].

- **Receptor Flexibility**

This is a major challenge in docking i.e., handling of flexible protein. A biomolecule/protein adopts different conformations depending upon the ligand to which it binds. This confirms that docking done with a rigid receptor will give a single conformation of receptor. However, when the docking is done with flexible receptor, the ligands may require many receptor conformations to bind. In molecular docking studies, usually the most neglected aspect is *different conformational* states of proteins. Since the protein flexibility is important as it accounts for better affinity to be achieved between a given a drug and target. Another aspect of target flexibility is active site water molecules. Water molecules must be rectified to avoid using artifact waters in the docking process [9].

- **Scoring Function**

Another challenge in docking is imperfection in scoring function. Just like search algorithm is having potential to give optimum conformation, scoring function should also be able to differentiate true binding modes from all the other parallel modes. A potential scoring function would be computationally much economical, unfavourable for analyzing several binding modes. When there is accuracy, scoring functions make number of suggestions to evaluate ligand affinity. The physical phenomenon i.e., entropy and electrostatic interactions are disregarded in scoring schemes. Hence the lack of suitable scoring function, both in terms of accuracy and speed, is the main congestion in molecular docking programming [10].

CONCLUSION

The potential docking method is done after carefully screening the target, ligands and docking method presentation. The ligand flexibility however is nearly resolved and does not create much difficultly though protein flexibility needs to be enhanced. Water molecules should be included to consider the hydrogen bonding with non-aqueous residues. It is obvious from docking literature that it has reached a significant amount of maturity and in this short review; we have focused on applications and challenges of molecular docking in brief.

The aim of a docking procedure is often the discovery of new lead candidates. The identification of an overall reliable and robust scoring function seems to be one of the main challenges to be addressed in the near future. New algorithms will rise to find innovative solutions to docking difficulties and overwhelmed the restrictions of newly developed scoring

functions. Especially the issue of protein flexibility and induced-fit motions of the protein will gain in significance over the coming years in the design and discovery of novel lead candidates by means of protein-ligand docking and scoring.

Regardless of all the indicated limitations, noteworthy progress in docking technology has been made in the recent past. Computational docking calculations are usually being performed at several stages of the drug discovery process. The power of docking calculations has been well-recognized by interdisciplinary teams in the pharmaceutical industry. As the field of docking-based virtual screening matures, this recognition will certainly increase. It is hoped that suitable and broadly accepted sets of test data will become well-known, that the methods will evolve to facilitate the comparisons required to define the new frontiers.

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